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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :		(11) International Publication Number:
A61F 2/02, A61K 9/50, 47/30	A1	WO 97/25936
		(43) International Publication Date: 24 July 1997 (24.07.97)

(21) International Application Number: PCT/US97/00215

(22) International Filing Date: 8 January 1997 (08.01.97)

(30) Priority Data:
08/587,616 17 January 1996 (17.01.96) US

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(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: BUFFERED RESORBABLE INTERNAL FIXATION DEVICES FOR REPAIR OF BONE FRACTURES

(57) Abstract

A bioerodible implantable material, comprising a bioerodible poly(lactide-co-glycolide) polymer that produces acidic products upon hydrolytic degradation, and a buffering compound that buffers the acidic products and maintains the local pH within a desired range. The buffer compound acts to reduce the inflammatory foreign body response generated by the acidic products and reduces the sterile abscess condition that occurs at the site of the bioerodible implant materials of the prior art. Materials made according to the invention may be used for internal fixation devices (IFDs) for bone repair.

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BUFFERED RESORBABLE INTERNAL FIXATION DEVICES FOR REPAIR OF BONE FRACTURES

FIELD OF THE INVENTION

This invention relates to the field of implantable internal fixation devices for repair of bone fractures, and more specifically to resorbable bone implant biomaterials which contain a buffering compound.

BACKGROUND OF THE INVENTION

The trend in internal fixation devices for repair of damaged bone is toward the use of resorbable, tissue compatible biopolymers. Biopolymers such as poly(glycolic acid) (PGA), poly(lactide) (PLA), and copolymers of lactic and glycolic acids, (poly(lactide-co-glycolide) or PLGA) have been used in the production of internal fixation devices, such as screws, pins, and rods to hold bone together following surgery, or to repair broken bones. Other polymers, such as poly(dioxanone), have also been considered for use in the manufacture of surgical internal fixation devices. However, it has been observed that tissue response to resorbable implants fabricated from these biopolymers is not uniformly acceptable (Bostman, J. Bone and Joint Surg. 73, 148-153 (1991)).

The tissue response to biopolymer-based implants has been well documented. Late sterile inflammatory foreign body response (sterile abscess) has been reported in about 8% of fractures repaired with these polymers (Bostman, supra). In a randomized study of 56 open reduction and internal fixation of malleolar fractures of the ankle with metal ASIF screws and plates or with rods of PLGA, two cases of sterile inflammatory wound sinus were observed 3 to 4 months after the operation in the injuries fixed with the polymer rods (Rokkanen et al., Lancet 1, 1422-1425 (1985); Bostman et al., J. Bone and Joint Surg., 69-B(4), 615-619 (1987)). Other

studies have also documented an inflammatory reaction following implantation of PGA or PLGA fixation devices. The fraction of patients suffering from this reaction ranges from 4.6 to 22.5% (Bostman et al., Clin. Orthop. 238, 195-203 (1989); Bostman et al., Internat. Orthop. 14, 1-8 (1990); Hirvensalo et al., Acta Orthop. Scandinavica, Supplementum 227, 78-79 (1988); Hoffman et al., Unfallchirurgie 92, 430-434 (1989); Partio et al., Acta Orthop. Scandinavica, Supplementum 237, 43-44 (1990); Bostman et al., Internat. Orthop. 14, 1-8 (1990)). The inflammatory reaction is not limited to poly(glycolide) polymers. Internal fixation devices made from poly(lactide) have also been observed to exhibit an inflammatory reaction. Eitenmuller et al. reports that 9 of 19 patients (47.7%) who had fractures of the ankle treated with absorbable plates and screws of poly(lactide) had an inflammatory response. (J. Eitenmuller, A. David, A. Pomoner, and G. Muhyr: "Die Versorgung von Sprunggelenlzsfrakturen unter Verwendung von Platten und Schrauben aus resorbserbarem Polymermaterial", Read at Jahrestagung der Deutschen Gesellschaft fur Unfallheilkunde, Berlin, Nov. 22, 1989).

In vitro studies have been performed to monitor pH changes as well as weight loss and the appearance of lactic acid from screws fabricated from poly(lactide-co-glycolide) with a lactide:glycolide ratio of 85:15. (Vert et al., J. Controlled Release 16, 15-26 (1991)). An induction period of about ten weeks was observed before any significant change in media pH or weight loss occurred. This time period corresponds to the induction periods of seven to twenty weeks noted by clinicians. However, no attempt has been made to alleviate the source of inflammation.

SUMMARY OF THE INVENTION

The invention is a bioerodible implantable material, comprising a bioerodible polymer that produces acidic products upon hydrolytic degradation, and a buffering

compound that buffers the acidic products and maintains the local pH within a desired range. The buffer compound incorporated into the material of the invention acts to neutralize the acidic degradation products which cause inflammatory foreign body response upon degradation of the bioerodible polymer. Thus, the invention reduces the sterile abscess condition that occurs in the bioerodible implant materials of the prior art. Materials made according to the invention may be used for internal fixation devices (IFDs) for bone repair.

The bioerodible materials and methods of the invention include a bioerodible polymer that forms acidic products as it degrades. The bioerodible polymer undergoes hydrolysis in the body and generates acidic products that cause irritation, inflammation, and swelling (sterile abscess formation) in the treated area. To counteract this effect, a buffer is included in the bioerodible material to neutralize the acidic degradation products and thereby reduce the sterile abscess reaction. The buffer included in the bioerodible material of the invention maintains the pH surrounding the area of surgery to approximately neutrality (i.e., pH 7), or any other pH chosen by the surgeon. Preferably, the pH is maintained in the range of 6-8, and more preferably in the range of 6.8-7.4.

According to the invention, the bioerodible material includes a bioerodible polymer that undergoes hydrolysis to produce acidic products when exposed to an aqueous medium. The bioerodible polymers useful in the invention include polydioxanone, poly(ϵ-caprolactone); polyanhydrides; poly(ortho esters); copoly(ether-esters); polyamides; polylactones; poly(propylene fumarates) (H[-O-CH(CH_3)-CH_2-O-CH=CH-CO-]$_n$OH); and combinations thereof. In a preferred embodiment, the polymer poly(lactide-co-glycolide) (H[-OCHR-CO-]$_n$OH, R=H, CH_3) (PLGA) is used. The PLGA polymers used according to the invention have a lactide to glycolide ratio in the range of 0:100% to 100:0%, inclusive, i.e., the PLGA

polymer can consist of 100% lactide, 100% glycolide, or any combination of lactide and glycolide residues. These polymers have the property of degrading hydrolytically to form lactic and glycolic acids.

The buffering compound included in the bioerodible material of the invention may be any base capable of reacting with the acidic products generated upon hydrolysis of the bioerodible polymer. Exemplary buffering materials that may be implemented according to the invention include the salts of inorganic acids, the salts of organic acids, or the salts of polymeric organic acids. Preferably, the calcium salts of weak acids are used, such as calcium carbonate, although calcium phosphates, calcium acetates, calcium citrates and calcium succinates may also be used. Preferably, the buffering compound has an acid dissociation constant that is smaller than the acid dissociation constant of the acidic products generated upon hydrolysis of the bioerodible polymer. Alternatively, the buffering compound preferably has a hydrolysis constant that is greater than the hydrolysis constant of the acidic products.

Preferably, the buffering compound included in the material of the invention is only partially soluble in an aqueous medium. In general, buffers of lower solubility are preferred because buffer loss from the polymer by diffusion will be minimized (Gresser and Sanderson, "Basis for Design of biodegradable Polymers for Sustained Release of Biologically Active Agents" in Biopolymeric Controlled Release Systems, Ch. 8, D.L. Wise, Ed., CRC Press, 1984).

The invention also includes methods of making a buffered bioerodible material for implantation into a surgical site. In one embodiment, the method according to the invention includes the steps of dissolving a bioerodible polymer in a solvent, and mixing a buffering compound with the dissolved bioerodible polymer, the buffering compound capable of buffering the acidic products within a desired pH range. The resulting mixture is cast into a sheet, and the solvent is

evaporated to produce a buffered bioerodible implantable material in film form. The resulting film may be further processed, for example, compacted under pressure, extruded through a die, injection molded, or shaped into a form useful for bone repair.

In another embodiment, the method according to the invention includes mixing dry, solid bioerodible polymer particles of a specific size with dry, solid buffering compound particles of a specific size, and mixing the bioerodible polymer particles and the buffering compound particles in a desired proportion. This mixture may then be processed as described above.

In another embodiment, the method of the invention includes providing an open celled bioerodible foam polymer of controlled density and providing a buffer dissolved in a solvent wherein the foam polymer is not soluble in the solvent, such as described in U.S. Pat. No. 5,456,917 to Wise et al., the whole of which is incorporated by reference herein. The buffer is loaded into the foam polymer, and the loaded foam polymer is freeze dried to remove the solvent. The resulting loaded bioerodible polymer may be further ground into particles of a predetermined size, extruded through a die, or shaped into useful forms.

In another embodiment, the method of the invention includes providing a bioerodible polymer having a melting temperature and producing acidic products upon hydrolytic degradation, providing buffer particles comprising buffer material coated with a polymer having a melting temperature greater than the melting temperature of the bioerodible polymer. The bioerodible polymer is heated to a temperature between the melting temperatures of the bioerodible polymer and the coating polymer, and the heated bioerodible polymer is mixed with the coated buffer particles. The mixture is then cooled and processed into useful forms.

As used herein, the term "bioerodible" is defined as the susceptibility of a biomaterial to degradation over time,

usually months. The term "buffer" is defined as any material which limits changes in the pH in the implant and its near environment only slightly upon exposure to acid or base. The term "acidic products" is defined herein as any product that has a pH less than 7.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to the field of internal fixation devices (IFD) used for surgical repair of orthopaedic and maxillofacial fractures. The invention is a bioerodible implantable material, comprising a bioerodible polymer capable of producing acidic products upon hydrolytic degradation, and a buffering compound that buffers the acidic products within a desired pH range.

The bioerodible material of the invention includes at least one bioerodible polymer that undergoes hydrolysis to produce acidic products when exposed to an aqueous medium. The bioerodible polymers useful in the invention include, but are not limited to, polydioxanone ($H[-O-CHR-CO-]_nOH$); poly(ϵ-caprolactone); polyanhy-drides; poly(ortho esters); copoly(ether-esters); polyamides; polylactones; poly(propylene fumarates) ($H[-O-CH(CH_3)-CH_2-O-CH=CH-CO-]_nOH$); and combinations thereof. A preferred polymer material useful in the invention is poly(lactide-co-glycolide) ($H[-OCHR-CO-]_nOH$, R=H, CH_3) with a lactide to glycolide ratio in the range of 0:100% to 100:0%. Accordingly, the PLGA polymer can consist of 100% lactide, 100% glycolide, or any combination of lactide and glycolide. This polymer has the property of degrading hydrolytically to form organic acids (lactic acid and glycolic acid) which accumulate in the region surrounding the implant.

The buffering compound included in the bioerodible material of the invention includes base capable of reacting with the acidic products generated upon hydrolysis of the bioerodible polymer. Exemplary buffering materials that may be implemented according to the invention include the salts

of inorganic acids, organic acids, or polymeric organic acids. Preferably, the calcium salts of weak acids are used, such as calcium carbonate, although calcium phosphates, calcium acetates, calcium citrates and calcium succinates may also be used.

In general, buffers of lower solubility are preferred because buffer loss from the polymer by diffusion will be slower (Gresser and Sanderson, supra). Preferably, the buffering compound has an acid dissociation constant that is smaller than the acid dissociation constant of the acidic products generated upon hydrolysis of the bioerodible polymer. Ionic buffers will, in general, be the salts of weak acids. The acid, of which the buffer is a salt, should have an ionization constant (acid dissociation constant, Ka) which is less than the Ka for the acid products of polymer hydrolysis. Alternatively, the buffering compound has a hydrolysis constant that is greater than the hydrolysis constant of the acidic products.

According to the invention, a preferred buffering compound is calcium carbonate. Upon reaction with an acid, calcium carbonate forms a calcium salt, carbon dioxide (CO_2), and water (H_2O) according to the following equation:

$$2R\text{-}CO_2H + CaCO_3 \longrightarrow (R\text{-}CO_2)_2Ca + H_2O + CO_2.$$

Gaseous carbon dioxide generated from the neutralization reaction is observed to be absorbed by the surrounding aqueous medium. The solubility of gaseous CO_2 in water at 760 mm Hg and 37°C is approximately 0.95 mg/ml (Merck Index, 1989). Thus, upon being generated *in situ*, gaseous CO_2 dissolves in and is eliminated from tissue fluids. In addition, free acid generation from the polymers of the invention proceeds slowly. Thus, degradation of the polymer component is the rate limiting step in the reaction, and even during the period of most rapid degradation, generation of acidic products occurs slowly. The slow rate of degradation

and associated acid production gives carbon dioxide ample time to dissolve in the surrounding fluids.

The amount of calcium carbonate required to be loaded into a bioerodible polymer matrix to neutralize a given quantity of lactic and glycolytic acids can be estimated by calculating the moles of monomeric acid produced at 100% hydrolysis. For PLGA of any composition (i.e., $-[-O-CH(CH_3)-CO-]_x-[O-CH_2-CO-]_{(1-x)}$, where x and y are the fractions of lactide and glycolide respectively, the molecular weight of the lactide component is 72 g/mol and the molecular weight of the glycolide component is 58 g/mol), the average monomer residue molecular weight is

$$72x + 58(1-x) = 14x + 58.$$

Thus, one gram of PLGA-50:50 (where x = 0.5) will generate approximately 0.0154 moles of monomeric acid upon hydrolysis. Referring to the neutralization reaction above, the amount of calcium carbonate buffer needed to neutralize this quantity of acid is 0.0077 moles, or 0.77 grams (mol. wt. of $CaCO_3$ = 100 g/mol). Thus, the fraction of calcium carbonate buffer loaded into the polymer matrix is 43.5% by weight. Similar determinations can be calculated for other polymer and buffer combinations and are within the skills of the ordinary skilled practicioner. Other calculations may also be made, for example, calculation of the amount of buffer required to neutralize a percentage of the acid groups generated upon hydrolysis.

An appropriate buffer should have a low aqueous solubility so that it will not be rapidly lost by dissolution. The basic component of the buffer (the anion) should react easily with the protons of the acid products of hydrolysis. Letting B^- represent the buffer anion and L^- the lactate (or glycolic) anion, the equilibrium can be expressed as:

$$HL + B^- \rightleftharpoons L^- + HB$$

In other words, HB must be a weaker acid than HL (or B^- must be a stronger base than L^-). These relationships may be expressed quantitatively by ionization constants of the respective acids (Ka):

$$Ka^{HB} < Ka^{HL}$$

Thus a viable buffer would be $CaHPO_4$ (dibasic calcium phosphate). The reaction of lactic acid with the anion, HPO_4 is:

$$HL + HPO_4^{-2} \rightleftharpoons L^- + H_2PO_4^-$$

The $H_2PO_4^-$ anion has an acid dissociation constant of approximately 6.31×10^{-8} whereas the various racemates of lactic acid have dissociation constants in the range of approximately 1.38×10^{-4} to 1.62×10^{-4}. Taking 1.5×10^{-4} as a mean value, the equilibrium constant for the above reaction may be calculated as:

$$K_{eq} = \frac{K_a^{HL}}{K_a^{H_2PO_4^-}} = 2.4 \times 10^3$$

Thus, the equilibrium lies to the right and protons produced by ionization of lactic or glycolic acids will be removed by the buffer.

Buffers are included in the polymer in solid form preferably should have a relatively small particle size, for example, between less than 1.0 and 250 μm. Particle size reduction can be accomplished by any standard means known in the art, such as ball milling, hammer milling, air milling, etc. If buffer and polymer are to be blended by the dry mixing method (described below), the polymer particle size must also be considered. Polymers such as the PLGAs have relatively low glass transition temperatures and melting temperatures. Thus, polymer particle size reduction must be

accompanied by cooling, for example using a Tekmar A-10 mill with a cryogenic attachment.

Following milling, the desired particle size range of the buffer and the polymer may be recovered by sieving through, for example, U.S. Standard sieves. Particles in the size ranges of <45, 45-90, 90-125, 125-180, 180-250 μm may be conveniently isolated.

In selection of particle size range, it is sometimes desirable to combine two or more ranges, or to use a wide range of sizes, for instance all sizes less than 250 μm. Larger particles may be preferred in some applications of the invention because larger particles take longer to be eroded by the acids and will therefore extend the useful lifetime of the buffer. In some cases particle size reduction will not be necessary, such as when commercially available precipitated calcium carbonate is used (e.g., Fisher Scientific, Inc., Catalog No. C-63)

Several methods may be used to incorporate the buffer into the polymer. These methods include solution casting coupled with solvent evaporation, dry mixing, incorporating the buffer into a polymer foam, and the polymer melt method.

Method 1. Solution Casting - Solvent Evaporation

This method may be used with buffers which are either soluble or insoluble in the solvent. The polymer is dissolved in any suitable volatile solvent, such as acetone, tetrahydrofuran (THF), or methylene chloride. The buffer, which may be soluble or insoluble in this solvent, is added to give the final desired ratio of polymer to buffer. If particle size reduction of the buffer is necessary, it may be accomplished by ball milling the suspension of buffer in the polymer solution. In contrast, if the buffer is soluble in the chosen solvent, particle size reduction at any stage is not necessary.

The suspension or co-solution is cast as a film on a glass or other inert surface, and the solvent is removed by

air drying. Residual solvent remaining in the film may be further removed by subjecting the film to vacuum drying at elevated temperatures. As an example, if calcium carbonate is to be used as a buffering compound and it is desired to neutralize 50% of the acid formed by hydrolysis of PLGA-50:50, the buffer content of the composition should be 27.8%.

In an exemplary embodiment, to prepare 50 grams of composite, 36.1 grams of PLGA-50:50 are dissolved in approximately 250 ml of tetrahydrofuran, and 13.9 grams of calcium carbonate of the desired particle size range is added to the solution mixture. After distributing the calcium carbonate homogeneously by mixing, the suspension is dried to a film as described above.

The resulting film may be processed by compaction under high pressure, extruded through a die, injection molded, or other method known in the art. Further definition of the final shape may be accomplished at this point by any desirable machining process, such as lathing.

Method 2. Dry-Mixing

A polymer of appropriate particle size range is mixed with the buffer, also of chosen particle size range, in proportions to give the desired stoichiometric buffering capacity. The dry mixture is thoroughly blended by rotating the mixture in a ball mill jar from which the grinding balls have been omitted, or other suitable mixing device. The blended mixture may then be processed by compaction, extrusion, injection molding, etc., as described above.

Method 3. Incorporating the Buffer into a Polymer Foam

This method deposits the buffer as microcrystals within the pores of a foamed polymer. An open celled polymer foam of controlled density may be formed by lyophilization of a polymer solution as described in U.S. Pat. No. 5,456,917 to Wise et al., the whole of which is incorporated by reference herein. For example, open celled PLGA-85:15 foams (i.e.,

foams with 85% lactide and 15% glycolide by weight) with different morphologies are created by lyophilization of frozen solutions of the polymer from either benzene or glacial acetic acid. The density and void volume of the foam is a function of the initial polymer solution as shown in TABLE 1.

TABLE 1

FOAM DENSITY AS A FUNCTION OF SOLUTION CONCENTRATION

Concentration of solution, mg/ml	Density of Foam, mg/cm_3
30.0	43.0
40.0	60.1
45.0	65.0
50.0	70.1±0.9
66.7	87.5

In this method, buffers which are soluble in a solvent which does not dissolve the polymer foam are preferred, such as water soluble buffers or low molecular weight alcohols, such as ethanol. The weight fraction of the buffer in the polymer/buffer composite, f, will depend on both absolute density of the polymer, d_p, the density of the foam, d_f, and the concentration of the buffer in the solvent, C. This dependency is given by the loading equation:

$$f = [1 + d_f d_p / C(d_p - d_f)]^{-1}$$

TABLE 2 shows loading of PLGA-85:15 foams prepared from acetic acid solutions with the anti-tuberculosis drug isoniazid dissolved in water. Results of these loading experiments are given in TABLE 2.

TABLE 2

INH CONTENT (WEIGHT PERCENT) IN FOAMS AS A FUNCTION OF INH SOLUTION CONCENTRATION AND FOAM DENSITY

INH Soln. Conc., mg/ml	Foam Density, mg/cm^3 43.0	70.1	87.5
13.0	20.0[a](22.8[b])	---	---
21.5	26.5 (32.8)	---	---
29.4	35.0 (44.0)	---	---
5.1	---	6.0 (6.5)	---
11.5	---	12.0 (13.6)	---
25.0	---	24.7 (25.5)	---
10.0	---	---	9.0 (9.8)
21.5	---	---	18.4 (18.9)
39.5	---	---	28.0 (30.0)

a) Measured values of loading.

b) Loadings as predicted by the loading equation.

A buffer solution comprising a chosen buffer in a suitable solvent is forced into the pores of the open celled foam by repeated cycles of evacuation (degassing) and repressurization (by emitting air at atmospheric pressure or higher). After the foam has been impregnated with the buffer solution, excess solution is drained off and the saturated foam is subjected to a second lyophilization to remove the solvent. Following this loading process, the polymer/buffer composite may be processed as described above.

Method 4. Polymer Melt

A known weight of the buffer is incorporated by mixing into a known weight of a suitable melted polymer. A quantity of polymer is heated to a temperature above its melting point, and a suitable buffer is blended into the melted polymer. The resulting polymer/buffer composite is

solidified by cooling, and may be processed as described above, or ground and sieved prior to processing.

In some applications, it may be desirable to protect the buffering compound, for example, during processing according to the melt method, or to make the buffering compound available at the later stages of polymer degradation. In such cases, it is desirable to coat the buffering compound particles with a material that degrades at a slower rate than the material chosen for the fixation devices. Thus, the buffering compound is exposed only after the body of the device and the coating material have partially degraded. Exemplary materials used to coat the buffering compound particles include high molecular weight poly(L-lactide) or poly(ϵ-caprolactone).

The particles of buffering compound may be coated with the protective material by any method that coats particles, such as spray coating with a solution of protecting polymer or microencapsulation. Alternatively, a chosen protective polymer may be made in a melted state and buffer particles are added. The melt is cooled and ground and milled to the desired particle size range. Alternatively, the buffering compound may be added to a solution of the protective polymer and removing the solvent by evaporation. The dried mass is compacted in a mold under high pressure and grinding or milling the compacted mass to the appropriate particle size range.

Although PLGA polymers are used in the preceeding examples, one of ordinary skill in the art will appreciate that other polymers, such as polydioxanone, poly(ϵ-caprolactone); polyanhydrides; poly(ortho esters); copoly(ether-esters); polyamides; polylactones; poly(propylene fumarates); and combinations thereof, may be similarly processed according to the methods of the invention. Moreover, selection of a particular polymer is based primarily on the known properties of the polymer such as the degree of cross-linking, polymer strength,

polymerization rate, rate of hydrolytic degradation, etc. One of ordinary skill in the art may take these and/or other properties into account in selecting a particular polymer for a particular application. Thus, such a selection of a particular polymer is within the skills of the ordinary skilled practioner.

Having showed the preferred embodiments, those skilled in the art will realize many variations are possible which will still be within the spirit and scope of the claimed invention. Therefore, it is the intention to limit the invention only as indicated by the scope of the claims.

CLAIMS

We claim:

1. A bioerodible implantable material, comprising:

a bioerodible polymer, said bioerodible polymer producing acidic products upon hydrolytic degradation; and

a buffering compound which buffers said acidic products within a desired pH range.

2. The bioerodible implantable material of claim 1, wherein said bioerodible polymer is selected from the group consisting of polydioxanone, poly(ϵ-caprolactone), polyanhydride, poly(ortho ester), copoly(ether-ester), polyamide, polylactone, poly(propylene fumarate), and combinations thereof.

3. The bioerodible implantable material of claim 1, wherein said bioerodible polymer comprises poly(lactide-co-glycolide) with a lactide to glycolide ratio in the range of 0:100% to 100:0% inclusive.

4. The bioerodible implantable material of claim 1, wherein said buffering compound is the salt of an inorganic acid.

5. The bioerodible implantable material of claim 1, wherein said buffering compound is the salt of an organic acid.

6. The bioerodible implantable material of claim 5, wherein said organic acid is polymeric.

7. The bioerodible implantable material of claim 1, wherein said buffering compound is selected from the group consisting of carbonates, phosphates, acetates, succinates, and citrates.

8. The bioerodible, implantable material of claim 1, wherein said buffering compound is a calcium salt.

9. The bioerodible, implantable material of claim 1, wherein said buffering compound is calcium carbonate.

10. The bioerodible implantable material of claim 1, wherein the parent acid of said buffering compound has an acid dissociation constant that is smaller than the acid dissociation constant of said acidic products.

11. The bioerodible implantable material of claim 1, wherein said buffering compound has a hydrolysis constant that is greater than the hydrolysis constant of said acidic products.

12. A method of making a buffered bioerodible, implantable material, comprising the steps of:

dissolving a bioerodible polymer in a solvent, said bioerodible polymer producing acidic products upon hydrolytic degradation;

mixing a buffer compound with said dissolved bioerodible polymer, said buffer capable of buffering said acidic products within a desired pH range;

casting said mixture; and

evaporating said solvent of said mixture to produce a buffered bioerodible implantable material.

13. The method of claim 12, wherein said bioerodible polymer is selected from the group consisting of polydioxanone, poly(ϵ-caprolactone), polyanhydride, poly(ortho ester), copoly(ether-ester), polyamide, polylactone, poly(propylene fumarate), and combinations thereof.

14. The bioerodible implantable material of claim 12, wherein said bioerodible polymer comprises poly(lactide-co-

glycolide) with a lactide to glycolide ratio in the range of 0:100% to 100:0% inclusive.

15. The method of claim 12, further comprising the step of milling said buffer compound in said polymer solution.

16. The method of claim 12, further comprising the step of processing said buffered bioerodible implantable material into a desired form.

17. The method of claim 12, further comprising the step of coating said buffer compound with a polymeric material that degrades at a slower rate than PLGA.

18. A method for making a buffered bioerodible implantable PLGA material, comprising the steps of:

providing bioerodible polymer particles having a specific size, said bioerodible polymer producing acidic products upon hydrolytic degradation;

providing buffer particles having a specific size, said buffer particles comprising a buffer capable of buffering said acidic products; and

mixing said bioerodible polymer particles and said buffer particles in a predetermined proportion.

19. The bioerodible implantable material of claim 18, wherein said bioerodible polymer particles comprise poly(lactide-co-glycolide) with a lactide to glycolide ratio in the range of 0:100% to 100:0% inclusive.

20. The method of claim 18, further comprising the step of processing said buffered bioerodible implantable material into a desired form.

21. The method of claim 18, further comprising the step of coating said buffer particles with a polymeric material that degrades at a slower rate than PLGA.

22. A method for making a buffered bioerodible implantable material, comprising the steps of:

providing an open celled bioerodible foam polymer of controlled density, said bioerodible foam polymer producing acidic products upon hydrolytic degradation;

providing a buffer compound dissolved in a solvent, said foam polymer not soluble in said solvent, said buffer compound capable of buffering said acidic products;

loading said buffer compound dissolved in said solvent into said PLGA foam polymer; and

freeze drying said buffer loaded foam polymer to remove said solvent.

23. The method of claim 22, further comprising the step of processing said buffered bioerodible implantable material into a desired form.

24. The method of claim 22, further comprising the step of coating said buffer particles with a polymeric material that degrades at a slower rate than PLGA.

25. The method of claim 22, wherein said bioerodible polymer comprises poly(lactide-co-glycolide) with a lactide to glycolide ratio in the range of 100:0 to 0:100 inclusive.

26. A method for making a buffered bioerodible implantable material, comprising the steps of:

providing a bioerodible polymer having a first melting temperature, said bioerodible polymer producing acidic products upon hydrolytic degradation;

providing buffer particles comprising buffer material coated with a protective polymer, said protective polymer

having a second melting temperature, said second melting temperature greater than said first melting temperature, said buffer particles comprising a buffer capable of buffering said acidic products;

heating said bioerodible polymer to a temperature between said first melting temperature and said second melting temperature;

mixing said heated bioerodible polymer and said coated buffer particles; and

cooling said mixture.

27. The method of claim 26, further comprising the step of processing said buffered bioerodible implantable material into a desired form.

28. The method of claim 26, wherein said bioerodible polymer comprises poly(lactide-co-glycolide) with a lactide to glycolide ratio in the range of 100:0 to 0:100 inclusive.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/00215

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61F 2/02; A61K 9/50, 47/30
US CL : 424/426, 501; 514/772.3
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/426, 501; 514/772.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,397,572 A (COOMBES ET AL) 14 March 1995, see column 6, lines 58-63; column 9, lines 1-17.	1-28

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 20 FEBRUARY 1997	Date of mailing of the international search report 06 MAR 1997
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Form PCT/ISA/210 (second sheet)(July 1992)*